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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/043,933 | 03/30/1998 | JEAN-MARC BALLOUL | 017753-094 | 7553 |

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| EXAMINER | |
|---|---|
| FOLEY, SHANON A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 11/05/2003

39

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/043,933 | BALLOUL ET AL. | |
| | Examiner | Art Unit | |
| | Shanon Foley | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *10-20,25-31,79,80,82,83,85-92,94,95,97,98,100-110 and 112-123* is/are pending in the application.

4a) Of the above claim(s) *10-20,25-31,86,100 and 112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79, 80, 82, 83, 85, 87-92, 94, 95, 97, 98, 101-110 and 113-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *32,35* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *39* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

In paper no. 33, applicant amended claims 79, 91 and 108, cancelled claims 99 and 111 and added new claims 120-123. Claims 10-20, 25-31, 79, 80, 82, 83, 85-92, 94, 95, 97, 98, 100-110 and 112-123 are pending in the application. Claims 10-20, 25-31, 86, 100 and 112 are withdrawn from consideration and claims 79, 80, 82, 83, 85, 87-92, 94, 95, 97, 98, 101-110 and 113-123 are under consideration.

### *Request for Continued Examination*

The request filed on 7/28/03 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/043933 is acceptable and a RCE has been established. An action on the RCE follows.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 79, 80, 82, 83, 85, 87-92, 94, 95, 97, 98, 101-110 and 115-119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claims 79, 91 and 108 recite the transitional claim language "consisting essentially of". It remains unclear which elements are intended to be excluded from the claimed compositions. The MPEP § 2111.03 states that "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as

equivalent to "comprising"." Therefore, the amended transitional phrase is interpreted as open claim language.

Applicant states that claims 79, 91 and 108 have been amended to recite the stimulation of specific immunity towards the papillomavirus. However, this phrase does not aid in clarifying which ingredients would materially affect the ingredients recited in the claims. Therefore, the rejection is maintained for reasons of record.

Claims 79 and 121 recite the phrase "to stimulate specific immunity towards the papillomavirus in the absence of specific immunity". This phrase is unintelligible. It is not clear how specific immunity is stimulated in the absence of specific immunity. This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 79, 80, 82, 83, 85, 87-90, 121, 122 and 123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Independent claims 79 and 121 recite "to stimulate specific immunity towards the papillomavirus in the absence of specific immunity". Applicant states that support for this amendment is found throughout the specification and original claims. Applicant specifically points to page 3, lines 17-23 for support. However, this excerpt from the specification discusses

the advantages the specific immunity induced by papillomavirus polypeptides and aspecific immunity induced by an immunostimulatory molecule. It is unclear where support for the amended phrase for stimulating specific immunity in the absence of specific immunity can be found. Applicant is requested to either identify a page and line number within the specification where support can be found or cancel the new matter. This rejection also affects dependent claims 80, 82, 83, 85 and 87-90.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 79 and 87-90 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Stanley et al. (US 6,096,869) for reasons of record.

Applicant states that claims 79, 91 and 108 have been amended to recite stimulation of specific immunity towards papillomavirus, which is not taught in the reference.

Applicant's arguments have been fully considered, but are found unpersuasive because the phrase recited in the claims is unintelligible. However, if the simulation of specific immunity towards papillomavirus is what applicant intends, Stanley et al. also anticipate this limitation because the compositions administered by Stanley et al. mount an immune response against tumors caused by papillomavirus infection, see column 14, lines 15-37.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 80, 82, 83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., in further view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

The claims are drawn to nononcogenic variants of E6 having amino acids 111-115 deleted and E7 having amino acids 21-26 deleted.

Stanley et al. do not teach the specific nononcogenic fragments of E6 or E7.

However, Crook et al. teaches that an amino acid deletion of residues 111-115 in E6 reduces binding to p53. Munger et al. teaches that the amino acid residues in HPV-16 E7 necessary to form a complex with retinoblastoma tumor suppressor gene is located surrounding the cysteine residue at position 24.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Stanley et al. teaches that the HPV proteins in the pharmaceutical formulation are also antigenic fragments, see the previous citations and the proteins comprising the specific residue deletions taught by Crook et al. and Munger et al. would be antigenic fragments. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 121 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (WO 96/11274), Galloway. (Infectious Agents and Disease. 1994; 3: 187-193).

The claim is drawn to a pharmaceutical composition consisting of E6, E7, L1 and L2.

Lowy et al. teach that papillomavirus L1/L2 capsid proteins are prophylactic. Rabbits immunized with virus-like particles composed of L1/L2 are protected from subsequent infectious papillomavirus challenge, see column 2, lines 47-59. Lowy et al. suggest incorporating papillomavirus E6 or E7 into compositions to provide a therapeutic effect, see column 2, line 60 to column 3, line 16 and column 7, lines 35-61. Lowy et al. teach inducing neutralizing antibodies against E7 in rabbits by inoculation with L1/L2 papillomavirus-like particles, example 9 in column 14.

Galloway teaches a prospect for prophylactic vaccine to treat papillomavirus infections with a composition that includes L1and L2 proteins and therapeutic vaccines that include E6 and

E7 proteins from the papillomavirus, see the abstract on page 187. Galloway also teaches that most individuals have antibodies that recognize the capsid proteins, especially L2, see the first paragraph of column 2 on page 189. In addition, rabbits immunized with L1 or L2 conferred protective immunity against the virus, see first full paragraph of column 2 on page 190. Galloway also teaches that L2 and E7 fusion proteins have reduced the number, severity, and duration of lesions. E7 was found to protect mice from a syngeneic tumor in an MHC-restricted fashion, see the paragraph bridging pages 190-191. Stimulation of the immune response against E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191. From the teachings of Galloway, one of skill in the art at the time of the invention would have been motivated to combine E6, E7, L1, and/or L2 into a vaccine to treat or prevent a papillomavirus infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7.

One of skill in the art at the time of the invention would have been motivated to combine therapeutic E6 and E7 proteins of Galloway and the L1 and L2 prophylactic proteins of Lowy et al. to treat and prevent papillomavirus infection in a host. One of skill in the art at the time of the invention would have had a reasonable expectation of success of producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Galloway). Therefore, the invention as a whole would have been prima facie obvious, absent unexpected results to the contrary.

Claims 91, 98, 101-107 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. supra, Galloway, supra, Bubenik et al. (International Journal of Oncology. March, 1996; 8: 477-481), Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

The claims are drawn to a pharmaceutical composition comprising HPV-16 polypeptides consisting essentially of and consisting of E6, E7, L1, and L2 in addition to an immunostimulatory molecule, IL-2.

The teachings of Lowy et al. and Galloway are incorporated herein.

Neither Galloway nor Lowy et al. teach the use of IL-2.

However, Bubenik et al. demonstrate that the use of IL-2 as an adjuvant enhances the immunization effect in Syrian hamsters immunized with irradiated HPV 16-transformed tumor cells expressing E6 and E7, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into a composition comprising the prophylactic L1 and L2 proteins of Lowy et al. and Galloway, and the therapeutic E6 and E7 proteins taught by Galloway, to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation inducing a specific immune response with a composition comprising the IL-2 of Bubenik et al. with the papillomavirus proteins of Lowy et al. and Galloway because Bubenik et al. specifically teach augmenting the function of vaccines against papillomavirus with IL-2, see "Adjuvant effect of IL-2 in mice..." and the discussion section on page 479. Therefore, the

invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

With respect to the only remaining reference at issue in the instant rejection, applicant argues that there is no suggestion in Galloway to combine HPV polypeptides with a cytokine.

Applicant's arguments have been fully considered, but are found unpersuasive because Bubenik et al. provide motivation to combine IL-2 with a papillomavirus vaccine composition because the cytokine enhances the immunization effect.

Lowy et al., Galloway and Bubenik et al. do not teach these non-oncogenic E6 or E7 proteins.

Crook et al. teaches that an amino acid deletion of residues 111-115 in E6 reduces binding to p53. Munger et al. teaches that the amino acid residues in HPV-16 E7 necessary to form a complex with retinoblastoma tumor suppressor gene is located surrounding the cysteine residue at position 24.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Galloway teach that E6 and E7 have ameliorative effects on papillomavirus infection and Crook et al. and Munger et al. teach E6 and E7 modifications to reduce detrimental effects.

Claims 108-110, 113-120 and 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galloway, Bubenik et al., Crook et al. and Munger et al., all supra.

The claims are drawn to a composition consisting essentially of or consisting of E6, E7 and IL-2. The E6 and E7 polypeptides have been mutated to delete specific amino acids.

Galloway teaches therapeutic vaccines that include E6 and E7 proteins from the papillomavirus, see the abstract on page 187. Galloway also teaches that stimulation of the immune response against E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191.

Galloway does not teach IL-2.

However, Bubenik et al. demonstrate that the use of IL-2 as an adjuvant enhances the immunization effect in Syrian hamsters immunized with irradiated HPV 16-transformed tumor cells expressing E6 and E7, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into a composition comprising the therapeutic E6 and E7 proteins taught by Galloway, to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation inducing a specific immune response with a composition comprising the IL-2 of Bubenik et al. with the papillomavirus proteins of Galloway because Bubenik et al. specifically teach augmenting the function of vaccines against papillomavirus with IL-2 in cells expressing E6 and E7, see "Adjuvant effect of IL-2 in mice..." and the discussion section on page 479.

Neither Galloway nor Bubenik et al. teach the instant mutations to E6 and E7.

However, Crook et al. teaches that an amino acid deletion of residues 111-115 in E6 reduces binding to p53. Munger et al. teaches that the amino acid residues in HPV-16 E7 necessary to form a complex with retinoblastoma tumor suppressor gene is located surrounding the cysteine residue at position 24.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate tumor suppressive effects of these proteins. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Galloway teach that E6 and E7 have ameliorative effects on papillomavirus infection and Crook et al. and Munger et al. teach E6 and E7 modifications to reduce detrimental effects. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

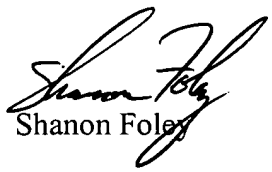
Applicant argues that the teachings of Munger et al. and Crook et al. do not remedy the deficiencies of the primary references. However, the instant combination of references do not possess any deficiencies.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Shanon Foley